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REVIEW

Effect of lifestyle, gender and age on collagen formation and degradation

Lars Tue Sørensen

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Abstract Historically, inappropriate lifestyle with an inadequate dietary intake of vitamin C has been associated with poor wound healing as a clinical manifestation of scurvy. In modern times, clinical evidence produced over the past few decades indicates that a modern lifestyle factor, such as smoking, together with biologic characteristics, like old age and male gender, are risk factors for abdominal wall hernia and recurrence. The pathologic pathways for these clinical observations are unclear. Yet, evidence from animal and human studies suggests that these exogenous and endogenous factors may have a negative impact on collagen metabolism, enhancing degradation and impairing formation.

Keywords Smoking · Gender · Age factors · Collagen · Collagenase · Vitamin C · Lifestyle factors · Wound healing · Hernia

Introduction

Deficient collagen formation due to inappropriate lifestyle among sailors, whose diet was short of fresh fruit and vegetables, was, for centuries, a devastating problem on sea voyages. After 10 weeks at sea on his 1497–1499 voyage to India around the tip of Africa, Vasco da Gama described that a large number of sailors were attacked by gingival and cutaneous swelling and bleeding and loss of teeth, predicting subsequent weakening and death. During a circumnavigation of the world in 1740–1744, where nine of ten sailors succumbed to scurvy, George Anson observed that "the scars of old wounds, healed for many years, were forced open again" [1]. James Lind, who in 1747 was the first to discover the beneficial effect of citrus fruits on scurvy, observed skin ulcers occurring from the spontaneous opening of previously damaged skin and the disruption of wounds following minimal trauma [2]. These descriptions are in accordance with the etymologic meaning of scurvy being "a disease that ruptures the belly" [3]. In fact, this is the exact meaning of the Danish name "skørbug," having the same Middle Low German origin as the English name "scurvy."

Eliminated at the present time, scurvy no longer constitutes a health hazard, as we have fully understood the importance of dietary intake of vitamin C—named ascorbic acid due to its antiscorbutic properties—being an essential co-factor in collagen biosynthesis and necessary for the maintenance of human life. However, increasing evidence over the past few decades suggests that the modern lifestyle, especially smoking together with biologic characteristics like old age and male gender, are, indeed, factors that may affect the balance between the formation and degradation of collagen and should be considered in the search for the complex aetiology of abdominal wall hernia formation and recurrence.

Formation of collagen

The biomechanical strength of the connective tissue which supports the abdominal wall depends largely on

L. T. Sørensen (✉)
Department of Surgery, Bispebjerg Hospital,
2400 Copenhagen NV, Denmark
e-mail: lts@dadlnet.dk

the content of mature collagen. Deficiency of collagen biosynthesis and ultrastructure may, therefore, lead to the formation of abdominal wall hernia and recurrence after hernia repair [4].

The biosynthesis of collagen is well described in the biochemical literature. In short, proliferating fibroblasts produce α-chains of about 1,000 amino acid residues, which are converted in the endoplasmic reticulum into the long rod-shaped molecules of procollagen. In an early crucial step with molecular oxygen as the substrate and vitamin C as the essential co-factor, the amino acids proline and lysine are hydroxylated into hydroxyproline and hydroxylysine, which form interchain hydrogen bonds that stabilise the triple-stranded helix of procollagen. As these amino acids are rarely found in proteins other than collagen, hydroxyproline is used as a specific biochemical marker for collagen.

Extracellularly, the procollagens are converted into collagen fibres through strong covalent bonds between lysine and hydroxylysine residues and are arranged head-to-tail in parallel bundles of three, helically intertwined with a characteristic 64-nm cross-striation. After formation, the fibres are remodelled and orientated in an orderly pattern to support the tensile strength of the tissue.

In the case of vitamin C deficiency, numerous large fibroblasts may be present [5], but proline and lysine are not being hydroxylated and the unstable and immature procollagen molecules are recognised as damaged and, therefore, destroyed before mature collagen fibres can be formed. Experimental studies of the effect of vitamin C deficiency on wound healing conducted on humans over 60 years ago revealed impaired healing and the disintegration of scars of experimental wounds after several months of dietary restrictions and subsequent normalization following vitamin C repletion. In one subject, the disruption of a 15-year-old appendectomy wound was reported [3].

Degradation of collagen

In the abdominal wall, as with other tissues, damaged collagen fibres are being repaired in a continuous controlled process of proliferation and remodelling. The normal turnover of collagen is very slow and it may persist for years before being degraded and replaced [6]. If the process of degradation is, for some reason, excessive, the structure of the supporting tissue of the abdominal wall becomes attenuated and the biomechanical strength of the tissue decreases, predisposing to the development of hernia.

Some matrix metalloproteinases (MMPs) and serine proteases are characterised as collagenases, which specifically degrade collagen. While retaining the structural integrity of the collagen fibres, they cleave specific proteins, allowing macrophages and fibroblasts to burrow through the thicket of collagen for tissue repair. This process is tightly regulated by the tissue inhibitor of metalloproteinases (TIMPs) to limit extensive damage during degradation. Of the main collagenases, fibroblast collagenase (MMP-1) plays a distinctive role in eliminating defective procollagens during the formation of new collagen fibres, whereas the neutrophil collagenases (MMP-8, MMP-9) are secreted as a result of an inflammatory response and are specifically important in the inflammatory phase of wound healing. The neutrophil-derived proteinases like collagenase and elastase have drawn specific interest, as they are believed to play a major role in tissue-destructive disorders like pulmonary emphysema, parodontosis and aortic aneurysms [7–9]. It is likely that abdominal wall hernia is a tissue-destructive disorder too, as suggested by Cannon and Read, considering the higher blood levels of elastin degrading activity and the lower level of proteinase inhibitors in patients with direct inguinal hernia [10].

Smoking

Over the past few decades, clinical studies have demonstrated that smokers have a higher incidence of postoperative wound ruptures, suggesting that smoking impairs wound healing and decreases the tensile strength of wounds. In a recently published large prospective series of 4,855 unselected patients undergoing different types of gastrointestinal surgery, we found that smokers have a 64% higher risk of postoperative wound infections and an 80% higher risk of postoperative disruption of wounds or sutured tissue within the first 30 days after surgery [11]. This confirms previous findings of smokers' higher incidence of anastomotic leakage following colorectal surgery, sternal disruption following coronary bypass surgery and impaired healing after plastic, dental and orthopaedic surgery [12–16].

Recent evidence suggests that, several years after surgery, smokers are more likely to have disruption of sutured fascia. In a follow-up study of 310 laparotomized patients, we found that smokers had a four times higher risk of incisional hernia independent of other risk factors [17]. Similarly, inguinal hernias are more likely to recur several years after hernia repair in smokers compared to non-smokers, independent of

sutured or mesh technique being used [18, 19]. Being evident that smoking is associated with abdominal wall herniation following previous surgery, it remains unclear whether smoking predispose to the formation of primary hernias too, as the performed studies are small and the results conflicting [20, 21].

Smoking seems to affect several pathogenic pathways of collagen formation and degradation. Knuutinen et al. found significantly less procollagens I and III levels in the suction blister fluid of smokers, suggesting reduced collagen biosynthesis in the normal skin of smokers [22]. Moreover, smokers have been found to accumulate less hydroxyproline in an ePTFE wound healing model than non-smokers, indicating reduced collagen biosynthesis during wound healing [23]. In smokers' suction blister fluid, a 100% higher level of the neutrophil collagenase MMP-8 but normal TIMP-1 levels have been found, suggesting increased collagen degradation in smokers' skin [22]. Whether fibroblast collagenase is affected as well is less clear, as one study found high levels of mRNA MMP-1 in the skin biopsies of smokers [24], whereas another did not find a significant difference between smokers and non-smokers in skin MMP-1 activity [22].

On cellular levels, smoking seems to have a detrimental effect on the function of fibroblasts and macrophages, indicating impaired wound healing potential. The monocyte, which is precursor of the macrophage, has, in smokers, only half the chemotactic response as in non-smokers [25]. Likewise, in vitro studies of fibroblast cell cultures treated with smoke extract have disclosed inhibition of fibroblast migration, decreased collagen production, increased MMP-1 and MMP-3 levels and unchanged TIMP-1 levels [26, 27].

The inflammatory response is increased in smokers compared to non-smokers, presumably due to a higher oxidative stress induced by smoking [28]. As a result, the neutrophil function is altered, with an increased cell count and enhanced chemotactic response but decreased bactericidal capacity [25]. The activated neutrophils secrete potent tissue-destructive enzymes, such as collagenases and elastase, thus, shifting the balance between proteinases and inhibitors, as illustrated by the higher MMP-8 and unchanged TIMP-1 levels in smokers' suction blister fluid [22]. Accordingly, the latter findings support the view of smoking as a predisposing factor for tissue-destruction.

Reduced tissue oxygenation has, for a long time, been regarded as the primary mechanism for impaired wound healing in smokers. Nicotine is believed to induce a central and peripheral release of epinephrine, which, in adequate doses, causes vasoconstriction of the peripheral vessels. Following smoking the blood flow in the peripheral tissue is reduced by as much as 40%, as shown in some studies [29]. In addition, carbon monoxide binds to haemoglobin with a 200 times higher affinity than that of oxygen, which reduces the oxygen fraction in the arterial blood and changes the oxygen dissociation curve, attenuating the release of oxygen from the haemoglobin molecule to the peripheral tissue. Further, atherosclerosis and chronic obstructive lung disease, which may decrease oxygen levels in the peripheral tissue, are more prevalent in smokers. Following the smoking of one cigarette, Jensen et al. found that the subcutaneous oxygen tension is reduced significantly for a period of 30–45 min [30]. Consequently, the authors hypothesised that persons who smoke throughout the day will suffer from permanently reduced tissue oxygenation. Due to the fact that molecular oxygen is a substrate for the hydroxylation of proline and lysine, others have suggested that reduced tissue oxygen may impair the formation of collagen [23]. Although being of significance in tissues with poor blood supply, such as tissue flaps used in plastic and reconstructive surgery, this mechanism has been challenged by us in a recent study, where three weeks of validated abstinence from smoking, which should be more than enough to normalise the tissue oxygen level, did not increase the accumulation of hydroxyproline in a subcutaneously implanted ePTFE wound healing model [31]. Interestingly, the use of transdermal nicotine patches by abstinent smokers increased the procollagen I level and disclosed a borderline significant increase of hydroxyproline, thus, confirming the findings of other studies showing a stimulatory effect of nicotine on wound healing [31, 32].

Due to the oxidative stress induced by smoking and the function of vitamin C as an anti-oxidant, smokers have a high turnover of vitamin C, which reduces the systemic pool by two-thirds [33]. In view of earlier experimental studies on the detrimental effect of vitamin C deficiency on wound healing, we are currently studying whether the reduced vitamin C levels of smokers play a role in the complex pathogenesis responsible for impaired collagen formation and wound healing in smokers.

Other lifestyle factors

There is no evidence that increased dietary intake, which characterises obese patients, affects collagen metabolism. Clinically, obesity appears to be a predictor for the recurrence of incisional hernia [34, 35], but the pathologic mechanism for this finding is unclear. Statistical interaction with postoperative wound

infections may explain this finding, since wound infections occur more frequently in obese patients [36]. As postoperative wound infection has a detrimental effect of wound healing, thus, affecting collagen formation and degradation, it is likely that it is wound infection rather than obesity that explains the reported findings. Accordingly, wound infection has been found to predict a four-fold higher risk of both incisional hernia and recurrence [17, 34].

The opposite, deficient dietary intake leading to malnutrition or scurvy, which has been described above, may be a result of psychiatric or behavioural disorders, such as schizophrenia, depression, anorexia nervosa or, more simply, because of poverty, nutritional ignorance or bizarre dietary beliefs, including food fads [3].

Excessive alcohol intake has not been reported to affect collagen formation or degradation. Yet, alcohol decreases the intestinal absorption of vitamin C and since heavy drinkers often consume little else other than alcohol, which does not contain vitamin C, alcoholism can lead to scurvy, thus, affecting collagen formation [3].

Age and gender

The effect of biologic characteristics such as age and gender on collagen formation and degradation is not obvious. It is evident, however, that inguinal hernia is mainly a males' disease and occur more frequently with increasing age [20]. The difference between the genders is partly due to a difference of embryological characteristics. It is puzzling, however, that one fifth of men pass into adulthood with a patent processus vaginalis, but less than half develop inguinal hernia [37, 38]. Furthermore, indirect inguinal hernia may appear first in a man over 40 years of age [37]. Whether these observations can be attributed to a specific biochemical effect of age and gender is unclear, as it has been demonstrated that structural abnormalities of the internal ring, acquired attenuation of transversalis fascia or abnormal muscle function accompanying a congenital defect contribute to the development of inguinal hernia [37, 39].

Likewise, acquired abdominal wall hernias, like incisional hernias, seem to be associated with both age and gender. In a recently published study, we found an increasing risk of incisional hernia with age and a two-fold higher risk of incisional hernia in men compared to women [17]. The latter finding confirms previous reports [40]. In contrast, other studies have not found age or gender to be associated with the recurrence of incisional or inguinal hernia [18, 19, 34, 35, 41]. Male patients with abdominal aortic aneurysm specifically demonstrate a high incidence of both primary and recurrent inguinal hernia accompanying a 30% risk of incisional hernia following open aneurysm repair [42–44]. Although smoking, a predictor of aortic aneurysm, incisional hernia and the recurrence of inguinal hernia, was not controlled for in any of the cited studies, some of the authors have suggested that men may have a defective connective tissue metabolism predisposing to abdominal aortic aneurysmal disease, as well as abdominal wall hernia formation and recurrence [44, 45].

Postoperatively, some clinical studies show that men have a higher risk of wound rupture or burst abdomen following abdominal surgery than women, as well as a higher risk of anastomotic leakage following rectal resection [46–48].

The cellular pathway for an altered collagen metabolism and wound healing in the elderly and in men is unclear. Skin collagen and bone mass undergo a parallel decline with aging [49] and, in human tendons, collagen cross-linking appears to be reduced by each decade of age [50]. In patients with direct hernia, however, studies of collagen ultrastructure in rectus sheath biopsies have disclosed a reduced diameter and periodicity of collagen fibres independent of muscular status or patient age [51].

In studies of wound healing, cutaneous incisional wounds have revealed an overall decrease in collagen I and III deposition in the wounds of old mice, a decrease in fibronectin, as well as delay in the inflammatory response, re-epithelialization and the appearance of extracellular matrix components [52]. In human studies of collagen formation during wound healing, Lenhardt et al. found that, within the first week after colorectal surgery, men over 45 years of age deposited 25% less collagen in an ePTFE wound healing model than younger men and borderline significantly less than age-matched women [53]. Recently, we found that healthy premenopausal women accumulate significantly more collagen than men, indicating a higher female collagen formation capacity [54]. Others have found that postmenopausal women deposit significantly less collagen than premenopausal women following surgery [55], supporting evidence of an age-dependent delay in acute wound healing in postmenopausal women [56, 57].

Collagen degradation seems to play a role in both male and female elderly patients as well. Thus, compromised healing has been found to be associated with persistently high postoperative levels of MMP-9 [58]. Similar findings have been obtained in skin biopsies

from elderly patients, which have demonstrated increased concentration and activity of proteases such as MMP-2 and MMP-9 [59]. Furthermore, reduced levels of the tissue inhibitor of MMPs (TIMP-1 and TIMP-2) have been found in elderly patients [60].

The complex cellular mechanisms for these findings are not clear, but the above-mentioned findings suggest that increasing age may shift the balance between the formation and degradation of collagen. Based on studies of cutaneous wounds treated with oestrogen, where changes in the inflammatory response in the early phases of wound healing were found, Ashcroft et al. have suggested that variation in female reproductive hormone levels may explain alterations in various specific elements of wound healing, including collagen formation and degradation [57].

Conclusion

Smoking, old age and male gender seem to be associated with the formation and recurrence of abdominal wall hernia, but larger scale epidemiologic studies are still needed to confirm the present evidence. The exact pathologic mechanisms are yet to be described and characterised in detail, but growing evidence indicates that these exogenous and endogenous factors have a negative effect on collagen metabolism, enhancing degradation and impairing formation.

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